IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Gervais *et al.*	Customer Number:	32425
Docket No.:	GOUD:031US	Confirmation No.:	5065
Serial No.:	10/611,803	Art Unit:	1615
Filing Date:	July 1, 2003	Examiner:	Levy, Neil S.
Title:	PHARMACEUTICAL DOSAGE FORM BEARING PREGNANCY-FRIENDLY INDICIA		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR §1.131

Dear Sir:

1. I, Éric GERVAIS, residing at 3420, carrefour boulevard, Laval, Quebec, declare and state that:

2. I am one of the co-inventors of the above-identified U.S. Patent Application entitled: "PHARMACEUTICAL DOSAGE FORM BEARING PREGNANCY-FRIENDLY INDICIA" (hereinafter "the application").

3. I understand that the publication of Mezaache *et al.*, US Patent Application No. 2003/0124184A1, is applied as prior art against claims 6 and 35 of the application in the Office Action dated May 29, 2008 ("hereinafter "the Office Action". I also understand that the applicable date for the subject-matter of this publication that is used in the Office Action is June 21, 2002, namely the filing date of Mezaache *et al.*

4. Enclosed Exhibit A corresponds to a summary of background information on the invention, setting out the tests that I and the other co-inventors designed and conducted in relation thereto, which summary was prepared and transmitted to our patent counsel

prior to June 21, 2002. The tests set out in Exhibit A have served as bases for Examples 1 and 2 of the application. The Exhibit A document was not published or otherwise publicly disclosed more than one year prior to the July 1, 2003 filing date of the application.

5. In accordance with common U.S. Patent Office practice on 37 CFR §1.131 Declarations (M.P.E.P. § 715.07), all indications of dates in the attached Exhibit A have been deleted.

6. It is clear from the showing provided by Exhibit A attached hereto that we conceived and reduced to practice the presently claimed invention prior to the June 21, 2002 filing date of the Mezaache publication (*supra*).

7. The undersigned further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.

Respectfully submitted,

5/10/2008
Date

Éric Gervais

EXHIBIT A

[redacted] Add method claims

RE : ***Second draft for a patent application regarding the design of a pregnant woman to be printed on solid oral medications to be used during pregnancy***

This new concept is based on the use of a pictogram applied on solid oral medications to be used during pregnancy. The effect will be to increase the efficacy of the treatment by reducing the perception of teratogenic risk, hence increasing the compliance with the medication.

- ***increase the perception of safety***
- ***reassuring the patient***
- ***reducing the perception of teratogenic risk***
- ***reduce the feeling of guiltiness from taking a drug during pregnancy***
- ***increasing compliance***
- ***increasing the efficacy of the medication***
- ***reducing hospitalization rates***
- ***reducing complications***

Since the Thalidomide disaster in the 60's, people have discovered the devastating effects that some drugs may have on the fetus if taken during pregnancy. Severe birth defects caused by the Thalidomide exposure during early pregnancy have left a teratogenicity stigma on all medications. In the study entitled "*Prevention of Unnecessary Pregnancy Terminations by Counselling Women of Drug, Chemical, and Radiation Exposure During the First Trimester*", (1989)[1], Koren showed that pregnant women exposed to drugs that are known to be non teratogenic, still perceive that their fetus or their born-to-be has a 24 % chance to suffer a major birth defect. This is about the same risk as an intra-uterine exposure to the Thalidomide, that is together with isotretinoin, the most potent teratogen known up-to-date. This shows the extent to which the perception toward the use of medication by pregnant women is negative.

Women are anxious and scared to take medications during pregnancy. When they do it, they feel guilty and fear to be blamed by their peers, and even by their partner, if the medication was to have adverse effects on the fetus.

Many pregnant women suffer from chronic conditions such as depression, hypertension or diabetes. They absolutely must continue their pharmacological treatment in order to carry their pregnancy to completion. Pregnant women are frequently given prescription medications. On the conference " Clinical Pharmacology during Pregnancy" held and sponsored by FDA and NICHD on December 4-5, 2000, it was reported that women under 35-years of age receive on an average three different medications during their pregnancy, while those over 35 years receive on an average five different medications to deal with their different medical conditions during their pregnancy (not counting those over the counter available medications).

Many studies have shown that women have a tendency to abruptly stop taking their medications as soon as they learn that they are pregnant, due to the fear of teratogenic

risk[2]. In most cases, the risk to the health of the mother and her baby is much higher if she stops or reduces her treatment than if she keeps taking required medications.

Pregnant woman is not only anxious and worried about the fetus, but also exposed to the pressures of her physician, her pharmacist, her family, her partner, her friends and the media when it comes to making the decision of medications use during pregnancy. Hence, this is a burden and very complex issue for her.

Fotheringham stated that patients who perceive their families or friends to be supportive are more adherent than patients whose family members are not seen to be supportive[3]. Even though the medication has been prescribed by a physician, if one of these elements of influence within the pregnant woman's environment is in disagreement with the fact that she takes the medication, chances are that she will stop taking it or reduce the dose significantly, to the point where it will become sub-therapeutic.

The pregnancy itself is a state of anxiety and worry for the safety of the fetus. Taking a medication can only add the burden to this state of mind. Most of the time, pregnant woman feels guilty to take a medication and to put her born-to-be at risk. The perception that all medications pose a risk for major birth defects is highly present in pregnant population. This was shown by Pole, in the study entitled "*Drug Labeling and Risk Perceptions of Teratogenicity: A Survey of Pregnant Canadian Women and Their Health Professionals*"[4]: whatever information is given to the pregnant woman on a medication, we will never bring her perception of teratogenic risk down to zero (i.e. the medication is totally safe). There will always be a residual doubt that the medication could potentially create malformations. Another author, Mazzotta, in the study entitled *"The perception of teratogenic risk by women with nausea and vomiting of pregnancy"*[5] showed that when a pregnant woman receives proper counselling on the real teratogenic risk of a medication, her perception of the teratogenic risk may be reduced by 36%. Therefore, there are ways to help pregnant women to decrease their anxiety toward medication use during pregnancy and increase their compliance.

Diclectin is the medication specifically labelled and prescribed to treat nausea and vomiting of pregnancy (NVP). It is the most studied drug in the world regarding its fetal safety (proven safe), but it bears the consequences from the fact that Thalidomide was also used to treat NVP. Therefore, pregnant women make a direct link between Thalidomide and Diclectin, even though they are two completely different drugs and have no active ingredients in common. The fact that Diclectin is delivered in the form of an oral tablet, just as Thalidomide, only increases women's fear when it comes to Diclectin's fetal safety.

NON-COMPLIANCE

Non-compliance with prescription drugs is a huge health problem for patients in general, and it costs billions of dollars every year to the health care system. For example, it is estimated that less than 25% of outpatients will complete a 10 days course of antibiotic therapy for a strep throat or otitis media.

Matsui[6] described that non-compliance with prescribed medication regimens may take many forms, including failure to fill the prescription, incorrect dosage, improper dosing interval, and premature discontinuation of the drug. The problem of non-compliance is magnified during pregnancy due to the importance of fetal safety.

Despite all the scientific evidence supporting Diclectin's fetal safety, pregnant women do not follow their physician's recommendation as to the adherence to Diclectin's dosage. In most cases, they reduce the dosage by half. In fact, they do not comply with the proper dosage of Diclectin to the point that some woman and some physicians thus believe that the medication is not effective. Therefore, non-compliance often results in a perception of product efficacy failure.

When a pregnant woman refuses a treatment or reduces the prescribed dosage of Diclectin, she often finds herself in a sub-therapeutic state. This prevents the medication from being effective and may aggravate the mother's condition to developing hyperemesis gravidarum (HG). HG is the most severe end of NVP, when a pregnant woman suffers from loss of > 5% of her pre-pregnancy body weight, dehydration, acid-base disturbances, ketonuria and electrolyte imbalance. At this stage, physicians use intravenous medications that are not labelled for use during pregnancy (and for which there are very few data on their fetal safety) in order to control maternal condition. The use of these medications poses an unnecessary risk to the fetus. If this last resort medication appears to be ineffective due to the deterioration of the woman's condition, a therapeutic abortion may be considerd[7].

RISK TO THE MOTHER

Whenever women delay or discontinue use of medications during pregnancy due the fears for fetal safety, this may result in worsening of the condition and hospitalization with use of multiple drug therapy. Furthermore, depending of the underlying condition, some of them may have serious consequences like suicidal ideation. Einarson showed in her study[2] on abrupt discontinuation of psychotropic drugs during pregnancy due to teratogenic fears, that 70.3% of women reported physical and psychological adverse effects to the point that 29.7% reported suicidal ideation (one third of them was hospitalized),

RISK TO CREATE BIRTH DEFECTS

It is evidence-base today that taking folic acid before the conception and during the first trimester of pregnancy may prevent up to 75% of congenital abnormalities: spina bifida and anencephaly. If pregnant women are not compliant with their folic acid treatment, as it has been evidenced, they are putting there unborn child at an increased risk to have a major birth defect.

The situation is even worse if pregnant woman has been on a drug therapy that interferes with folic acid receptors (e.g., phenobarbital, phenytoin, carbamazapine, valproic acid). In this case, pregnant woman is even at greater risk for having a baby with birth defect if she is not compliant.

STUDIES

A study was conducted with 12 pregnant women This study was aimed at testing if a design printed on a tablet may have a positive impact on the efficacy of a drug taken during pregnancy, and if it is the case, which kind of design?
Different designs printed on a tablet were used, which would potentially increase the patients' confidence to take the tablet during pregnancy by reducing the teratogenic risk perception and improve the compliance in order to achieve better efficacy of the treatment. (Unpublished, internal company's data).

The study revealed that only the design representing a pregnant woman with her hand on her pregnant belly would be helpful to significantly increase the perception of fetal safety by reducing the level of maternal anxiety created by medication use during pregnancy. The design would indicate in a clear and precise fashion that the medication has been specifically designed for the pregnant woman. This is also reducing the feeling of guiltiness of taking a drug during pregnancy. This will reduce also the negative perception from her partner and or entourage regarding the use of medications during pregnancy

Improving patient's compliance may result in the effective treatment and subsequent reduction of visits to the physician, hospitalizations and complications.

During this study, pregnant women were also asked in regards to which colours would be preferable to make them feel better to increase the efficiency of the design. They chose strong, but relaxing colours to be better (Considering there state), they do not like colours that are too aggressive, especially on a white pill or tablet. Three colours have emerged from this study: purple – because it is relaxing, feminine and attractive, blue – because it is relaxing and discrete, and strong pink – because it symbolizes femininity.

SECOND STUDY

To validate the concept, we conducted an observational, prospective survey on pregnant women in family practice offices and obstetrician offices. The tool used for measuring the objective of the study (how reassured about fetal safety woman feels taking one or the other tablet once prescribe to them) was a validated scientific tool for subjective measurements: a visual analog scale (VAS) from 1-5 (1 being the least safe and 5 being the most safe). They were explained that the drug is safe for use in pregnancy and asked to label on the VAS how reassured about fetal safety they feel taking the tablet. They were shown two different tablets, one plane white and the other white, with a printed pregnant woman on it.

We collected data from 132 women and the results are shown in the table:

Test: Two-Sample Assuming Equal Variances

	Plain	With pregnant women	
Observations	132	132	
Mean	2,5227	3,6969	
Variance	1,2132	1,3120	
P(T<=t) one-tail			P< 0.0001

The study clearly showed superiority of the tablet with a printed pregnant woman concerning the perception of the teratogenic risk (results were statistical significant with

p<0.0001). Need further explanation. P= 1/10,000 chance to be wrong. Usually 0.05 is medically acceptable.

Pregnant women in this cohort felt 23.4% more reassured about the fetal safety to take the tablet with a printed pregnant woman, than plain one. If we project this result onto compliance and assume that the compliance would improve for the same 23.4%, it is not difficult to conclude how important the appearance of pregnant woman on the tablet is (unpublished, internal company's data).

HEALTH PROFESSIONAL PERCEPTION

After the Thalidomide disaster, physicians and pharmacists became very anxious about their liability associated with prescription or dispense of medications to pregnant women. In the study by Pole[4], it was shown that even health care professionals, after reading four different labels (all of them stating that drug is safe to be used in pregnancy), have evaluated these labels, as bearing a residual risk. They were unable to perceive or accept that medication is safe to be used in pregnancy.

Therefore, a design of the tablet with appearance of a pregnant woman with her hand on her pregnant belly, specifically to be used during pregnancy, will increase the patients' feeling of safety, comfort of taking medication during pregnancy and help in physicians' and pharmacists' perception of lower liability risk regarding prescribing and dispensing drugs for use in pregnancy.

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[1] Koren G., Pastuszak A., *Prevention of Unnecessary Pregnancy Terminations by Counselling Women on Drug, Chemical, and Radiation Exposure During the First Trimester*, Teratology 1990;41(6):657-61

[2] Einarson A., Selby P., Koren G., *Abrupt discontinuation of psychotropic drugs during pregnancy: fear of teratogenic risk and impact of counseling*, J. psychiatry Neurosci 2001; 26(1): 44-48

[3] Fotheringham MJ., Sawyer MG., *Adherence to recommended medical regimens in childhood and adolescence*. J Paediatr Child Health 1995;31(2):72-8

[4] Pole M., Einarson A., Pairaudeau N.& al., *Drug Labeling and Risk Perceptions of Teratogenicity: A Survey of Pregnant Canadian Women and Their Health Professionals*, J Clin.Pharmacology 2000;40: 573-577

[5] Mazzotta P., Magee L.-A., Maltepe C. & al., *The perception of teratogenic risk by women with nausea and vomiting of pregnancy*. Reproductive Toxicology 1999;13:313-319

[6] Matsui D., *Drug compliance in pediatrics: Clinical and research issues*. Ped Clin N Amer 1997;44(1):1-14

[7] Mazzotta P., Stewart D., Koren G., Magee LA. *Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy*. J. Psychosom Obstet Ginaecol. 2001;22(1):7-12